

# Processing and Process Controls

*Quality Assurance Workshop*

*February 15-17, 2005*

Mary Malarkey, Director

Office of Compliance and Biologics Quality



# OVERVIEW

- Old vs. the New – many similarities
- Walk through the new regulations and comments
- 2002 Guidance for Industry – still applicable?
- Validation vs. verification
- Microbial methods
- 361 vs. 351

## §1270.31(d)

- There shall be written procedures prepared, validated and followed for prevention of infectious disease contamination and cross-contamination by tissue during processing.

## § 1270.3(p)

- ◆ *Processing* means any activity performed on tissue, other than tissue recovery, including preparation, preservation for storage, and/or removal from storage to assure the quality and/or sterility of human tissue. Processing includes steps to inactivate and remove adventitious agents.

## § 1270.31(e)

Any facility may use current standard written procedures such as those in a technical manual prepared by another organization, provided the procedures are consistent with and at least as stringent as the requirements in this part. (*Verification*)

# 1271- Definitions

- § 1271.3(e)

*Manufacture* means, but is not limited to, any or all steps in the recovery, processing, storage, labeling, packaging, or distribution of any human cell or tissue, and the screening or testing of the cell or tissue donor.

# 1271-Definitions

- § 1271.3(ff)

- ◆ *Processing* means any activity performed on an HCT/P, other than recovery, donor screening, donor testing, storage, labeling, packaging, or distribution, such as testing for microorganisms, preparation, sterilization, steps to inactivate or remove adventitious agents, preservation for storage, and removal from storage.

# Comparison of Processing

## § 1270.3(p) vs. § 1271.3(ff)

- ◆ any activity performed on tissue, other than tissue recovery, including preparation, preservation for storage, and/or removal from storage to assure the quality and/or sterility of human tissue. Processing includes steps to inactivate and remove adventitious agents.
- any activity performed on an **HCT/P**, other than recovery, **donor screening, donor testing, storage, labeling, packaging, or distribution, such as testing for microorganisms,** preparation, **sterilization,** steps to inactivate or remove adventitious agents, preservation for storage, and removal from storage.

# 1271 - Definitions

- § 1271.3(kk)

- ◆ *Validation* means confirmation by examination and provision of objective evidence that particular requirements can consistently be fulfilled. Validation of a process, or process validation, means establishing by objective evidence that a process consistently produces a result or HCT/P meeting its predetermined specifications.

# 1271 - Definitions

- § 1271.3(11)
  - ◆ *Verification* means confirmation by examination and provision of objective evidence that specified requirements have been fulfilled

## § 1271.145

- Prevention of introduction, transmission, or spread of communicable diseases
  - ◆ You must recover, **process**, store, label, package, and distribute HCT/Ps, and screen and test cell and tissue donors, in a way that prevents the introduction, transmission, or spread of communicable diseases.

# Processing and Process Controls

## § 1271.220

- Core GTP requirements

- ◆ (a) General. If you are an establishment that processes HCT/Ps, you must process each HCT/P in a way that does not cause contamination or cross-contamination during processing, and that prevents the introduction, transmission, or spread of communicable disease through the use of the HCT/P.

# Comments

- One comment that FDA is requiring that HCT/Ps be sterile and processes be validated to assure sterility; concern that would impair function
  - ◆ We responded that this is not the case; however, we expect aseptic technique and control of activities to limit introduction of disease agents.
  - ◆ Will revisit as technology progresses

## § 1271.220

- (b) Pooling. Human cells or tissue from two or more donors must not be pooled (placed in physical contact or mixed in a single receptacle) during manufacturing.
- c) In-process control and testing. You must ensure that specified requirements, consistent with paragraph (a) of this section, for in-process controls are met, and that each in-process HCT/P is controlled until the required inspection and tests or other verification activities have been completed, or necessary approvals are received and documented. Sampling of in-process HCT/Ps must be representative of the material to be evaluated.

# Comments cont.

- Prohibition on Pooling
  - ◆ Some comments agreed; some didn't
  - ◆ FDA took to TSEAC for advice
  - ◆ Consistency with pooling provisions for blood products for certain HCT/Ps
- Prohibition in final rule; however, §1271.155 allows submission of request for exceptions or alternatives

## Comments cont.

- No comments on in-process test provision; however, we point out certain facts in preamble based on previous cases.
  - ◆ Sample selected for testing must be representative.
  - ◆ May not be the case for a small piece of HCT/P (companion tissue) processed along with the HCT/P and cultured
  - ◆ Reference to CDC MMWR and recommendation for combination of destructive and surface testing.

## § 1271.220

- (d) Dura mater. (1) When there is a published validated process that reduces the risk of transmissible spongiform encephalopathy, you must use this process for dura mater (or an equivalent process that you have validated), unless following this process adversely affects the clinical utility of the dura mater. (2) When you use a published validated process, you must verify such a process in your establishment.

# Comment cont.

## ■ Dura mater

- ◆ Number of comments to remove based on TSE risk
- ◆ We disagreed as would eliminate safeguards in place
- ◆ We agreed that no validated process currently exists that would not impact clinical utility; however, such process may be available in future

# Process Changes

## § 1271.225

- Any change to a process must be verified or validated in accordance with Sec. 1271.230, to ensure that the change does not create an adverse impact elsewhere in the operation, and must be approved before implementation by a responsible person with appropriate knowledge and background. You must communicate approved changes to the appropriate personnel in a timely manner.

# Process Validation

## § 1271.230

- (a) General. Where the results of processing described in Sec. 1271.220 cannot be fully verified by subsequent inspection and tests, you must validate and approve the process according to established procedures. The validation activities and results must be documented, including the date and signature of the individual(s) approving the validation.

# Comments cont.

- Process validation/verification
  - ◆ Our response to two comments on removal of the term “fully” from the phrase “fully verified” included a recommendation for validated microbiological methods including bacteriostasis and fungistasis testing
  - ◆ Reference to CDC MMWR

## § 1271.230

- (b) Written representation. Any written representation that your processing methods reduce the risk of transmission of communicable disease by an HCT/P, including but not limited to, a representation of sterility or pathogen inactivation of an HCT/P, must be based on a fully verified or validated process.

# Comment cont.

## ■ Label claims

- ◆ Now “written representations”
- ◆ May be based on “fully verified” as well as validated process
- ◆ QUESTION FOR INDUSTRY – can sterility or other pathogen inactivation for HCT/Ps be fully verified with current methodologies?
- ◆ More discussion needed in this area

## § 1271.230

- (c) Changes. When changes to a validated process subject to paragraph (a) of this section occur, you must review and evaluate the process and perform revalidation where appropriate. You must document these activities.

# Guidance for Industry

- “Guidance for Industry: Validation of Procedures for Processing of Human Tissues Intended for Transplantation,” March 2002.
- Still applicable in concept.
- Speaks of validation and verification

# Guidance for Industry

- Then (2002) current expectations with regard to viruses, bacteria, fungi and TSE-associated prions
- 21 CFR 1271.150(a) defines communicable diseases as including but not being limited to “those transmitted by viruses, bacteria, fungi, parasites and transmissible spongiform encephalopathy agents.”

# Guidance for Industry

- 21 CFR 1270.31(d) Procedures prepared, validated and followed to prevent contamination or cross contamination of tissue during processing by viruses, bacteria and fungi.
- 21 CFR 1270.31(e) Any facility may use current standard written procedures such as those in a technical manual prepared by another organization, provided the procedures are consistent with and at least as stringent as the requirements in this part.

# Guidance for Industry

- 21 CFR 1271.220(a) you must process each HCT/P in a way that does not cause contamination or cross-contamination during processing, and that prevents the introduction, transmission, or spread of communicable disease through the use of the HCT/P.
- 21 CFR 1271.230(a) Where the results of processing described in Sec. 1271.220 cannot be fully verified by subsequent inspection and tests, you must validate and approve the process according to established procedures. The validation activities and results must be documented, including the date and signature of the individual(s) approving the validation.

# How is Process Validated?

- Know input, e.g. possible bioburden (number) and desired output, e.g. log reduction of organisms detected at end of process by validated methods
- Develop protocol including what will be tested and what specific results should be achieved (acceptance criteria). The protocol should include multiple runs to demonstrate consistency.
- Consider spiking studies based on worst-case to determine log reduction of process as a whole.

# How is Process Validated?

- Were predetermined acceptance criteria met?
  - ◆ YES – process may be considered acceptably validated . Still need to test product.
  - ◆ NO – determine what went wrong; flaw in process or in study. Make appropriate change(s); new protocol, new study.
- “Life cycle” approach to validation

# How is a Process Verified?

- Example: sterilization of processing instruments using accepted industry standard cycle.
  - ◆ Cycle parameters verified each time
    - ◆ Pressure, time, temperature
  - ◆ Biological indicators used in each load
    - ◆ “kill” confirmed
- More monitoring/testing (e.g. BIs) required than for validated process
- Is it realistic for certain processes?

# Going back to...

- Definition of processing.....includes testing for microorganisms
- What is the best method or combination of methods for 361 HCT/Ps?
- Much work done by industry to address this difficult question.
- More discussion needed.

# Do you have a 351 product?

- Process validation an expectation under 21 CFR Parts 210-211
- Much discussion on this topic internally and externally
- Agency workgroup formed to update 1987 Guideline for Process Validation based on current thinking of life-cycle approach and emerging technologies for continuous process monitoring for certain products – not necessarily applicable for HCT/Ps

# More Information

- CBER External Web site:

- ◆ [www.fda.gov/cber](http://www.fda.gov/cber)

- Division of Case Management

- Blood and Tissue Compliance Branch

- ❖ 301-827-6201